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EXAMINER	
ROMEO, D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/287,500	Applicant(s) Lee et al.
	Examiner David Romeo	Group Art Unit 1647

☒ Responsive to communication(s) filed on *23 Oct 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *69-101* is/are pending in the application.

Of the above, claim(s) *72, 73, 81, 82, 88, and 92-101* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *69-71, 74-80, 83-87, and 89-91* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *69-101* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election without traverse of the species bone repair and the species IGF-I in Paper No. 6 is acknowledged.

2. Claims 72, 73, 81, 82, 88, 92-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 69-71, 74-80, 83-87, 89-91 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) to the extent that they are drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

3. Claims 69-71, 74-80, 83-87, 89-91 are being examined to the extent that they read upon the elected species.

Claim Objections

4. Claim 76 is objected to because of the following informalities: it appears that "TGF-b" should be "TGF-β". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 69-71, 74-80, 83-87, 89-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing bone formation, does not reasonably provide enablement for a method of inducing tissue formation, repair, or integration without regard to the tissue whose formation, repair, or integration is induced or for a method of treating a tissue degenerative condition without regard to the tissue treated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed to or encompass the induction, formation, and repair of all conceivable tissues. However, the functional activity of closely related TGF-β family members appears to be unpredictable. Kingsley (v7) discloses that TGF-β3 has 78% and 82% amino acid identity with TGF-βs 1 and 2, respectively (Table 1). Shah (w7) discloses that exogenous addition of recombinant TGF-β3 or neutralization of TGF-β 1 or TGF-β2 enhances healing and reduces scarring of cutaneous wounds and suggest the use of TGF-β3 as an anti-scarring agent (Abstract). Therefore, isoform specific differences exist in the role of the TGF-βs in wound healing and cutaneous scarring. Vukicevic (x7) teaches that OP-1 promotes cell condensations and tubulogenesis in metanephric mesenchyme but BMP-2, a closely related member of the TGF-β

superfamily, and TGF-β1 had no effect (page 9023, paragraph bridging columns 1-2). Shah, and Vukicevic establish that closely related members of the TGF-β superfamily have unpredictable effects. Furthermore, as noted by Nathan (y7) many cytokines that subserve familiar functions postnatally play different or unknown roles embryologically and given the amino acid sequence of a cytokine and any of its actions one cannot predict when or where it will do what else (page 981, paragraph bridging columns 1-2). Furthermore, the claims encompass the regeneration of permanent cells that are retained throughout adult life and seem never to divide and which cannot be replaced if lost, such as almost all nerve cells, the muscle cells of the heart, the auditory hair cells of the ear, and the lens cells of the eye. See Alberts (z7), pages 1142, last full paragraph, and pages 1144-1145. Although most permanent cells renew their parts, the claims encompass the growth of permanent cells, which cannot be replaced if lost. The specification fails to provide guidance for, or working examples of, regenerating permanent cells, which cannot be replaced if lost. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the unpredictability in the art it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 86 recites the limitation "the dimer" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 90 is indefinite over the recitation of "present at a concentration of" because it is unclear where the compound is "present" at the particular concentrations. The metes and bounds of the claim(s) are not clearly set forth.

Claim 91 is indefinite over the recitation of "protein comprises OP-1 at a concentration of" and over the recitation of "factor comprises IGF-I at a concentration" because the "protein" and "factor" are compounds and they are not compositions comprising the "protein" or "factor" at a particular concentration. The metes and bounds of the claim(s) are not clearly set forth.

Claim 91 is indefinite because is unclear what substance is present such that the number of ng of "protein" or "factor" per "ml" of substance could be determined. The metes and bounds of the claim(s) are not clearly set forth.

Claims 69, 74, 75, 77-80, 83-87, 89-91 are indefinite because they lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved; an intended use is not the same as achieving a result; in the absence of a recitation as to any result, or a process step producing a result, it is unclear what result of the process can be inferred.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 69-71, 77-80, 83-87, 89 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang (b7)[1].

Wang (b7) teaches that BMP-2 (wherein BMP is bone morphogenic protein) may be used to induce bone formation, provides pharmaceutical compositions containing a therapeutically effective amount of a BMP-2 in a pharmaceutically acceptable vehicle or carrier, the compositions further include at least one other therapeutically useful agent such as the BMP proteins BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, the compositions may also include an appropriate matrix for instance, for supporting the composition and providing a surface for bone growth, and teaches

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[1]Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

the administration of a BMP-2 in conjunction with at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, and the administration of a BMP-2 with other growth factors (paragraph bridging columns 2-3). It is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Further therapeutic methods and compositions of the invention therefore comprise a therapeutic amount of at least one BMP-2 with a therapeutic amount of at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7. Such combinations may comprise separate molecules of a BMP or heteromolecules comprised of different BMP moieties. For example, a method and composition of the invention may comprise a disulfide linked dimer comprising a BMP-2 and another "BMP". Further, BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I (column 6, lines 5-57; column 7, lines 7-42).

Inducing bone formation by providing a pharmaceutical composition containing a therapeutically effective amount of a BMP-2, IGF-I, and an appropriate matrix is a method comprising implanting a morphogenetic device in a mammal wherein the morphogenetic device comprises an implantable biocompatible carrier, a morphogenetic protein disposed in the carrier, and a MPSF, with the proviso that when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is activin, the MPSF may not be estrogen or calcitonin; when

the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a BMP homodimer or TGF-β, the MPSF may not be FGF, IGF-II, PDGF, estrogen, calcitonin or vitamin D; when the progenitor cell is an osteoblast stimulated to form bone or cartilage and the morphogenic protein is a BMP homodimer, the MPSF may not be TGF-β; and when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a homodimer of BMP-2 or BMP-3, the MPSF may not be parathyroid hormone. The morphogenetic device is implanted at a locus accessible to at least progenitor cell of the animal absent evidence to the contrary.

Wang also teaches a therapeutic method and composition for repairing fractures and other conditions related to cartilage and/or bone defects or periodontal diseases (column 6, lines 10-13). A therapeutic method for repairing fractures and other conditions related to cartilage and/or bone defects or periodontal diseases is a method comprising implanting at a locus that is a jaw bone for use in periodontal procedures, or at a locus that is a bone defect that is a fracture.

Wang also teaches that BMP-2 polypeptides of the invention may also be useful in the treatment of osteoporosis (sentence bridging columns 5-6). Osteoporosis is a degenerative condition of bone tissue.

The IGF-I is present in an amount capable of synergistically stimulating the ability of the BMP to induce bone formation because "[i]t is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors", and as evidenced by

Baylink (a7) (discussed below and incorporated herein by reference), and absent evidence to the contrary.

11. Claims 77, 85, 89 are rejected under 35 U.S.C. 102(e) as being anticipated by Kuberasampath (e7). Kuberasampath (e7) provides methods and compositions for inhibiting loss of bone mass, and/or for stimulating bone formation in mammals, particularly humans which includes administering to the individual a therapeutically effective morphogen in an amount and for a time sufficient to inhibit the loss of bone mass, and/or to increase bone mass in the individual. (column 3, lines 15-25). The morphogens may be administered together with other "co-factors" known to have a beneficial effect on bone remodeling, including IGF-I (column 4, lines 58-65). OP-1 is a useful morphogen (paragraph bridging columns 4-5). Kuberasampath (e7) teaches that rat osteoblasts were prepared and cultured in a multi-well plate as described for Example 2. In this example a 24-well plate was used. The cultured cells then were divided into three groups: (1) wells which received varying concentrations of morphogen; (2) wells which received varying concentrations of a local-acting growth factor; and (3) a control group which received no growth factors. In this example OP-1 was the morphogen tested at the following concentrations: 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium; and TGF-B was the local-acting growth factor, tested at 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium. The cells then were incubated for 72 hours. After the incubation period the cell layer was extracted with 0.5 ml of 1% Triton

X-100. The resultant cell extract was centrifuged, 100 µl of the extract was added to 90 µl of paranitrosophenylphospate (PNPP)/glycerine mixture and incubated for 30 minutes in a 37 °C water bath and the reaction stopped with 100 µl NaOH. The samples then were run through a plate reader (e.g., Dynatech MR700 plate reader, and absorbance measured at 400 nm, using p-nitrophenol as a standard) to determine the presence and amount of alkaline phosphate activity. Protein concentrations were determined by the Biorad method. Alkaline phosphatase activity was calculated in units/µg protein, where 1 unit=1 nmol p-nitrophenol liberated/30 minutes at 37 °C. The results, shown in FIG. 4, illustrate that morphogen alone stimulates the production of alkaline phosphatase in osteoblasts, and thus promotes the growth and expression of the osteoblast differentiated phenotype. In the figure, squares represent OP-1 concentrations, and diamonds represent TGF-β concentrations. See column 27, lines 4-33; Figure 4; column 14, lines 8-10. The compounds provided therein can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable nontoxic excipients and carriers. As noted above, such compositions may be prepared for parenteral administration, particularly in the form of liquid solutions or suspensions; for oral administration, particularly in the form of tablets or capsules; or intranasally, particularly in the form of powders, nasal drops, or aerosols. See column 23, full paragraph 1. The IGF-I is present in an amount capable of synergistically stimulating the ability of the OP-1 to induce bone formation as evidenced by Wang (b7) (discussed above and

incorporated herein by reference) and as evidenced by Baylink (a7) (discussed below and incorporated herein by reference), and absent evidence to the contrary.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 74, 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (b7) in view of Kuberasampath (c7).

Wang (b7) teaches that BMP-2 (wherein BMP is bone morphogenic protein) may be used to induce bone formation, provides pharmaceutical compositions containing a therapeutically effective amount of a BMP-2 in a pharmaceutically acceptable vehicle or carrier, the compositions further include at least one other therapeutically useful agent such as the BMP proteins BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, the compositions may also include an appropriate matrix for instance, for supporting the composition and providing a surface for bone growth, and teaches administration of a BMP-2 in conjunction with at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, and the administration of a BMP-2 with other growth factors (paragraph bridging

columns 2-3). It is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Further therapeutic methods and compositions of the invention therefore comprise a therapeutic amount of at least one BMP-2 with a therapeutic amount of at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7. Such combinations may comprise separate molecules of a BMP or heteromolecules comprised of different BMP moieties. For example, a method and composition of the invention may comprise a disulfide linked dimer comprising a BMP-2 and another "BMP". Further, BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I (column 6, lines 5-57; column 7, lines 7-42).

Inducing bone formation by providing a pharmaceutical composition containing a therapeutically effective amount of a BMP-2, IGF-I, and an appropriate matrix is a method comprising implanting a morphogenetic device in a mammal wherein the morphogenetic device comprises an implantable biocompatible carrier, a morphogenetic protein disposed in the carrier, and a MPSF, with the proviso that when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is activin, the MPSF may not be estrogen or calcitonin; when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a BMP homodimer or TGF-β, the MPSF may not be FGF, IGF-II, PDGF, estrogen, calcitonin or vitamin

D; when the progenitor cell is an osteoblast stimulated to form bone or cartilage and the morphogenic protein is a BMP homodimer, the MPSF may not be TGF-β; and when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a homodimer of BMP-2 or BMP-3, the MPSF may not be parathyroid hormone. The morphogenetic device is implanted at a locus accessible to at least progenitor cell of the animal absent evidence to the contrary.

Wang also teaches a therapeutic method and composition for repairing fractures and other conditions related to cartilage and/or bone defects or periodontal diseases (column 6, lines 10-13). A therapeutic method and for repairing fractures and other conditions related to cartilage and/or bone defects or periodontal diseases is a method comprising implanting at a locus that is a jaw bone for use in periodontal procedures, or at a locus that is a bone defect that is a fracture.

Wang is silent with respect to implanting a matrix comprising allogeneic bone.

Kuberasampath (c7) teaches that the substantially pure osteogenic protein is useful in clinical applications only in conjunction with a suitable delivery or support system (matrix). The matrix is made up of particles or porous materials. The pores must be of a dimension to permit progenitor cell migration and subsequent differentiation and proliferation. The particle size should be within the range of 70-850 μm, preferably 70-420 μm. It may be fabricated by close packing particulate material into a shape spanning the bone defect, or by otherwise structuring as desired, a material that is biocompatible (non-inflammatory) and, biodegradable in vivo to serve as

a "temporary scaffold" and substratum for recruitment of migratory progenitor cells, and as a base for their subsequent anchoring and proliferation. Useful matrix materials comprise collagen, homopolymers and copolymers of glycolic acid and lactic acid, hydroxyapatite, tricalcium phosphate and other calcium phosphates, and particulate, demineralized, guanidine extracted, species-specific (allogeneic) bone. See column 3, lines 31-50. Kuberasampath is silent with respect to inducing bone formation by providing a pharmaceutical composition containing a therapeutically effective amount of a BMP-2, IGF-I, and an appropriate matrix. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to induce bone formation by providing a pharmaceutical composition containing a therapeutically effective amount of a BMP-2, IGF-I, and an appropriate matrix, as taught by Wang, and to modify that teaching by substituting an appropriate matrix with the particulate, demineralized, guanidine extracted, species-specific (allogeneic) bone, as taught by Kuberasampath, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this substitution because particulate, demineralized, guanidine extracted, species-specific (allogeneic) bone is a useful matrix material for the implantation of osteogenic polypeptides. The invention is prima facie obvious over the prior art.

14. Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rueger (d7) in view of Wang (b7).

Rueger teaches that a prosthetic device, such as an artificial hip replacement device, e.g., a metallic device made from titanium, for example, is first coated with an osteogenic material which induces bone ingrowth. When the device is subsequently implanted into the individual, bone growth around the site of the implant is enhanced, causing a strong bond to form between the implant and the existing bone. The present method results in enhanced biological fixation of the prosthesis in the body, which is particularly important for weight bearing prostheses. Prostheses defining a microporous surface structure are locked in place as bone formation occurs within the micropores. The metal or ceramic prosthesis may itself define such a structure, or the prosthesis may be coated to provide an adherent porous surface. Materials useful for this purpose include, for example, collagen, homopolymers of glycolic acid, lactic acid, and butyric acid, including derivatives thereof; and ceramics such as hydroxyapatite, tricalcium phosphate or other calcium phosphates. Combinations of these materials may be used. A substantially pure osteogenic protein is then bound to the uncoated or coated prosthesis. Alternatively, the osteogenic protein can be mixed with the coating material, and the mixture adhered onto the surface of the prosthesis. See paragraph bridging columns 3-4. Titanium frequently is used to fabricate metal prostheses. The surface of these prostheses comprise a layer of titanium oxide. Therefore, titanium oxide itself was evaluated for its ability to serve as a carrier for OP-1 and in general for its biocompatibility with the bone formation process. The in vivo biological activity of implants containing a combination of titanium oxide and OP-1 (Sequence ID No. 1, residues 293-431) was

examined in rat subcutaneous and intramuscular assays. Implants contained 0, 6.25, 12.5, 25 or 50 μg of OP-1 formulated onto 30 mg of titanium oxide. See column 13, lines 49-60. Rueger is silent with respect to providing on a surface of the prosthetic device an osteogenic composition comprising OP-1 and IGF-I.

Wang (b7) teaches that BMP-2 (wherein BMP is bone morphogenic protein) may be used to induce bone formation, provides pharmaceutical compositions containing a therapeutically effective amount of a BMP-2 in a pharmaceutically acceptable vehicle or carrier, the compositions further include at least one other therapeutically useful agent such as the BMP proteins BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, the compositions may also include an appropriate matrix for instance, for supporting the composition and providing a surface for bone growth, and teaches administration of a BMP-2 in conjunction with at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, and the administration of a BMP-2 with other growth factors (paragraph bridging columns 2-3). It is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Further therapeutic methods and compositions of the invention therefore comprise a therapeutic amount of at least one BMP-2 with a therapeutic amount of at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7. Such combinations may comprise separate molecules of a BMP or heteromolecules comprised of different BMP moieties. For example, a method and composition of the invention may comprise a disulfide linked dimer comprising a BMP-2 and another "BMP". Further, BMP-2s, such as BMP-2A and BMP-2B, may

be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I (column 6, lines 5-57; column 7, lines 7-42).

Inducing bone formation by providing a pharmaceutical composition containing a therapeutically effective amount of a BMP-2, IGF-I, and an appropriate matrix is a method comprising implanting a morphogenetic device in a mammal wherein the morphogenetic device comprises an implantable biocompatible carrier, a morphogenetic protein disposed in the carrier, and a MPSF, with the proviso that when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is activin, the MPSF may not be estrogen or calcitonin; when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a BMP homodimer or TGF-β, the MPSF may not be FGF, IGF-II, PDGF, estrogen, calcitonin or vitamin D; when the progenitor cell is an osteoblast stimulated to form bone or cartilage and the morphogenic protein is a BMP homodimer, the MPSF may not be TGF-β; and when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a homodimer of BMP-2 or BMP-3, the MPSF may not be parathyroid hormone. The morphogenetic device is implanted at a locus accessible to at least progenitor cell of the animal absent evidence to the contrary.

Wang also teaches a therapeutic method and composition for repairing fractures and other conditions related to cartilage and/or bone defects or periodontal diseases (column 6, lines 10-13). A therapeutic method and for repairing fractures and other conditions related to cartilage and/or bone defects or periodontal diseases is a method comprising implanting at a locus that is a jaw bone for use in periodontal procedures, or at a locus that is a bone defect that is a fracture.

Wang is silent with respect to providing on a surface of a prosthetic device an osteogenic composition comprising OP-1 and IGF-I. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to provide on a surface of a prosthetic device an osteogenic composition comprising OP-1, as taught by Rueger, and to modify that teaching by using an osteogenic composition comprising OP-1 and IGF-I, as taught by Wang, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because BMPs may be combined with other agents beneficial to the treatment of the bone defects, such as various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF), such as IGF-I. The invention is prima facie obvious over the prior art.

15. Claims 77, 89-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath (e7) as applied to claim 77 above and further in view of Hock (w7) and further in

view ~~of~~ Baylink (a7) or Wang (b7). Kuberasampath (e7) provides methods and compositions for inhibiting loss of bone mass, and/or for stimulating bone formation in mammals, particularly humans which includes administering to the individual a therapeutically effective morphogen in an amount and for a time sufficient to inhibit the loss of bone mass, and/or to increase bone mass in the individual. (column 3, lines 15-25). The morphogens may be administered together with other "co-factors" known to have a beneficial effect on bone remodeling, including IGF-I (column 4, lines 58-65). OP-1 is a useful morphogen (paragraph bridging columns 4-5). The compounds provided therein can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable nontoxic excipients and carriers. As noted above, such compositions may be prepared for parenteral administration, particularly in the form of liquid solutions or suspensions; for oral administration, particularly in the form of tablets or capsules; or intranasally, particularly in the form of powders, nasal drops, or aerosols. See column 23, full paragraph 1. Kuberasampath (e7) teaches that rat osteoblasts were prepared and cultured in a multi-well plate as described for Example 2. In this example a 24-well plate was used. The cultured cells then were divided into three groups: (1) wells which received varying concentrations of morphogen; (2) wells which received varying concentrations of a local-acting growth factor; and (3) a control group which received no growth factors. In this example OP-1 was the morphogen tested at the following concentrations: 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium; and TGF-B was the local-acting growth factor, tested at 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium. The cells then

were incubated for 72 hours. After the incubation period the cell layer was extracted with 0.5 ml of 1% Triton X-100. The resultant cell extract was centrifuged, 100 µl of the extract was added to 90 µl of paranitrosophenylphospate (PNPP)/glycerine mixture and incubated for 30 minutes in a 37 °C water bath and the reaction stopped with 100 µl NaOH. The samples then were run through a plate reader (e.g., Dynatech MR700 plate reader, and absorbance measured at 400 nm, using p-nitrophenol as a standard) to determine the presence and amount of alkaline phosphate activity. Protein concentrations were determined by the Biorad method. Alkaline phosphatase activity was calculated in units/µg protein, where 1 unit=1 nmol p-nitrophenol liberated/30 minutes at 37 °C. The results, shown in FIG. 4, illustrate that morphogen alone stimulates the production of alkaline phosphatase in osteoblasts, and thus promotes the growth and expression of the osteoblast differentiated phenotype. In the figure, squares represent OP-1 concentrations, and diamonds represent TGF-β concentrations. See column 27, lines 4-33; Figure 4; column 14, lines 8-10. Kuberasampath (e7) is silent with respect to a method of treating osteoporosis with OP-1 as the morphogen at the following concentrations: 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium; and IGF-I as the local-acting growth factor at 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium.

Hock teaches that 10^{-8} M IGF-I increases the bone matrix apposition rate (Table 1; Figure 6). 10^{-8} M IGF-I is equal to 75 ng of IGF-I per ml. 75 ng of IGF-I per ml is "about 50 ng/ml" as recited in claim 91. Hock does not teach a method of treating osteoporosis with OP-1 as the morphogen at the following concentrations: 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium; and IGF-

I as the local-acting growth factor at 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml medium. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat osteoporosis by administering OP-1 together with other "co-factors" known to have a beneficial effect on bone remodeling such as IGF-I in a pharmaceutical acceptable carrier, as taught by Kuberasampath (e7), and to modify that teaching by administering 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml of OP-1, as taught by Kuberasampath (e7), together with 75 ng/ml IGF-I, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because OP-1 at a concentration of 0.1, 1.0, 10.0, 40.0 or 80.0 ng/ml promotes the growth and expression of the osteoblast differentiated phenotype and IGF-I at a concentration of 75 ng/ml increases the bone matrix apposition rate and because OP-1 may be administered together with other "co-factors" known to have a beneficial effect on bone remodeling, such as IGF-I. Although Kuberasampath (e7) in view of Hock are silent with respect to the synergistic action of OP-1 and IGF-I, no difference is seen between a synergistic combination of the two, the concentrations recited in the instant claims, and the concentrations taught by the prior art. Burden is shifted to Applicants to distinguish between the two.

Alternatively, Baylink (a7) teaches promoting bone growth and healing of osseous defects with a composition comprising a matrix capable of delivering the composition to the site of the bone defect and providing a structure for inducing bone formation, for example hydroxyapatite, said composition further comprising a BMP and growth factors, namely FGF, TGF-β, IGF-II, and

PDGF (column 1, lines 14-60). A composition with a content of at least two of the substances from the group consisting of the growth factors FGF, TGF-β, IGF-II, PDGF, and BMP not only has an additive effect on the proliferation and differentiation of bone cells, but creates a surprisingly marked synergism as well. One of ordinary skill in the art would have a reasonable expectation that a composition comprising OP-1 and IGF-I would not only have an additive effect on the proliferation and differentiation of bone cells, but would create a surprisingly marked synergism as well. One of ordinary skill in the art would be motivated to optimize the concentrations of OP-1 and IGF-I in order to create a surprisingly marked synergism because the same effect could be achieved with lower amounts of OP-1 and IGF-I thereby lowering the cost of treatment and/or lessening the likelihood of any untoward side-effects of the OP-1 and IGF-I.

One of ordinary skill in the art would have a reasonable expectation that the IGF-I would be present in an amount capable of synergistically stimulating the ability of the OP-1 to treat osteoporosis as evidenced by Wang (b7) (discussed above and incorporated herein by reference).

The invention is prima facie obvious over the prior art.

Information Disclosure Statement

16. The information disclosure statement filed 04/07/1999 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the list must be submitted in a separate paper. A separate list is required so that it is easy to confirm that applicant intends to submit an information

disclosure statement and because it provides a readily available checklist for the examiner to indicate which identified documents have been considered. A copy of a separate list will also provide a simple means of communication to applicant to indicate the listed documents that have been considered and those listed documents that have not been considered. Use of either form PTO-1449, Information Disclosure Citation, or PTO/SB/08A and 08B, Information Disclosure Statement, is encouraged. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ A(1) and ¶ C(1).

Although Applicants indicate that copies of the cited documents were enclosed with the IDS filed in U.S. patent application serial number 09027873, the cited documents are not present in the 09027873 application. If Applicants wish to have the information considered, Applicants are kindly requested to provide copies of the non-U.S. patent literature cited.

Conclusion

17. No claims are allowable.

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JANUARY 9, 2001